CLINICAL STUDY PROTOCOL: INDV-2000-104

Protocol Title: An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants

Protocol Number: INDV-2000-104

Original Protocol Date: 15 December 2022

Amendment Number/Date: Amendment 1/ 10 April 2023

NCT: NCT05694533

Clinical Study Protocol

PROTOCOL TITLE:

An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants

Protocol Number: INDV-2000-104

Amendment Number: 1

Amendment Scope: Global

Product: INDV-2000

Short Title:

Study of potential CYP3A4 induction by INDV-2000 in healthy adults

Study Phase: Phase I

Acronym: DDI Study

Sponsor Name: Indivior Inc.

Legal Registered Address:

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Regulatory Agency Identifier Number(s)

Registry	Identifying Number
IND	145881

Approval Date: 10 Apr 2023

Sponsor Signatories:

MEDICAL MONITOR NAME AND CONTACT INFORMATION

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

Protocol Number: INDV-2000-104

Protocol Title: An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants

The information contained in this protocol and all other information relevant to this study drug is the confidential and proprietary information of Indivior, and except as may be required by local laws or regulation, may not be disclosed to others without prior written permission of Indivior.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. My staff and/or I will conduct this study as outlined herein, in accordance with the regulations stated in the International Council on Harmonisation E6/Good Clinical Practice (ICH E6/GCP) guidelines and will make a reasonable effort to complete the study within the time designated.

I agree to ensure all associates, colleagues, and employees delegated to assist with the conduct of the study are trained on this study protocol and amendments, and other study-related materials, and are qualified to perform their delegated tasks. I will provide all study personnel copies of the protocol and any amendments, and grant access to all information provided by Indivior or specified designees. I will discuss the material with them to ensure that they are fully informed about INDV-2000 and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date**
Amendment 1	10 Apr 2023
Original Protocol	15 Dec 2022

Amendment 1 (10 Apr 2023)

Rationale for the Amendment:

[redacted]

Section Number and Name	**Description of Change**	**Brief Rationale**
[redacted]		

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	aspartate aminotransferase
AST	alanine aminotransferase
BID	twice daily
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF/eCRF	Case Report Form/Electronic Case Report Form
CYP	cytochrome P450
DDI	drug-drug interaction
DORA	dual orexin receptor antagonist
ECG	electrocardiogram
EOS	End of study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practices
GMR	Geometric mean ratio
HBsAg	hepatitis B surface antigen
HCl	hydrochloride
HIV	human immunodeficiency virus
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation

IEC	Independent Ethics Committee
IgM	immunoglobulin M
IND	investigational new drug
INR	International normalised ratio
IRB	Institutional Review Board
IV	intravenous
[redacted]	[redacted]
OUD	opioid use disorder
OX1R/OX2R	orexin-1/orexin-2 receptor
PK	Pharmacokinetic(s)
QTcF	heart rate-corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VAS	visual analogue scale
WONCBP	Women of nonchilbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants

Short Title:

Study of potential CYP3A4 induction by INDV-2000 in healthy adults

Regulatory Agency Identifier Number(s):

Registry	Identifying Number
IND	145881

Rationale:

[redacted]

Objectives and Endpoints

Table 1 Objectives and Endpoints

Objective	Endpoint
Primary	
• To determine changes in primary pharmacokinetic (PK) parameters (maximal and overall plasma exposure) of midazolam and 1-hydroxymidazolam following repeated oral doses of INDV-2000	• C_{max}, $AUC_{0-\infty}$, and AUC_{last} of midazolam and 1-hydroxymidazolam following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
Secondary	
• To assess the safety and tolerability of repeated oral doses of INDV-2000 alone and in combination with midazolam as determined by adverse event (AE) reporting	• Safety and tolerability of INDV-2000 as determined by AE reporting (incidence, seriousness, severity, and relatedness of treatment emergent adverse events [TEAEs])
Tertiary/Exploratory	

[redacted]

Overall Design Synopsis:

This is an open label, single-centre, fixed-sequence study in healthy adult participants.

Brief Summary:

The purpose of this study is to evaluate the CYP3A induction potential of INDV-2000 using midazolam as a sensitive substrate.

Participants who meet the eligibility criteria will be admitted to the study site on Day -1, and will remain confined until after the 24-hour blood draw and/or study procedures on Day 16.

On Day 1, participants will receive a single oral dose of midazolam syrup. On Days 2-15, participants will receive INDV-2000 BID with a single oral dose of midazolam syrup co-administered on Day 15.

[redacted]

Participants who received all doses of study drugs will return to the study site 7±2 days after the last dose for end of study (EOS) procedures, and to determine if any AE has occurred since the last study visit. Participants who terminate the study early will be asked to complete EOS procedures at the time of early termination in place of an EOS visit. Participants will be encouraged to stay up to 24 hours after the last dose to complete early termination assessments.

Number of Participants:

Approximately 20 participants will be assigned to receive the study drugs. This sample size is based on earlier clinical experience and is expected to provide at least 16 evaluable participants, [redacted]

Note: A participant will be considered enrolled at the time he/she receives the first dose of study drug.

Study Treatment and Duration:

On Day 1, participants will receive a single oral dose of 5 mg midazolam.

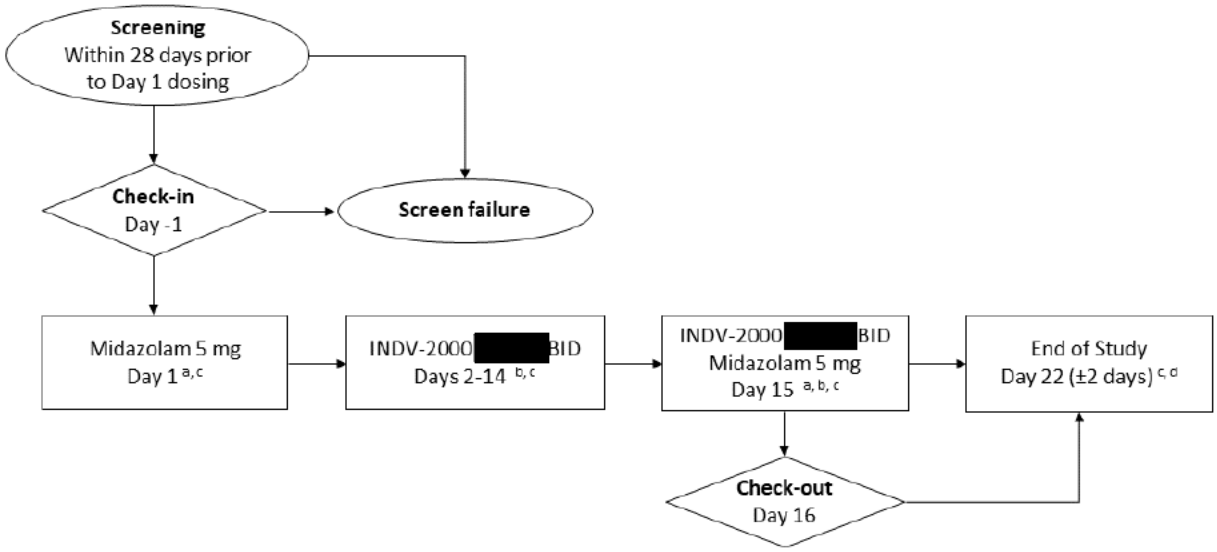
On Days 2-15, participants will receive [redacted] INDV-2000 BID (approximately every 12 hours) with a single oral dose of 5 mg midazolam co-administered with the morning INDV-2000 dose on Day 15.

The total planned study duration (screening to EOS) for each participant will be approximately 7 weeks. This includes a screening period of up to 4 weeks (ie within 28 days prior to dosing on Day 1), a treatment period of approximately 2 weeks (Days 1 to 16), and an EOS visit approximately 1 week from last dose (7±2 days).

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1 Study Schema



[redacted]

c. Safety assessments throughout the study

d. Participants who received all doses of study drugs will return to the study site 7±2 days after the last dose for EOS procedures, and to determine if any AEs have occurred since the last study visit. Participants who terminate the study early will be asked to complete EOS procedures at the time of eary termination in place of an EOS visit. Participants will be encouraged to stay up to 24 hours after the last dose to complete early termination assessments.

1.3 Schedule of Events (SoE)

Figure 2 Schedule of Events (SoE)

Study Procedures [1]	Screening [2]	Treatment Period (Days)																	EOS/ET
		-1 [3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Informed consent	X																		
Inclusion and exclusion criteria	X	X																	
Demography	X																		
Medical history	X																		
Full physical examination including height and weight [5]	X	X																X	X [4]
Testicular examination (males only) [6]	X																	X	X [4]
COVID-19 screen		X																	
HIV, Hepatitis B, and Hepatitis C (antibody)	X																		
Drug and alcohol screen	X	X																	X [4]
Serum pregnancy test (females only)	X																		
Urine pregnancy test (females only)		X																X	X [4]
Serum FSH (PMP (females only)	X																		
Haematology, serum chemistry [7], urinalysis	X	X		X [8]		X [8]				X [8]				X [8]			X [8]	X	X [4]
Coagulation	X			X [8]						X [8]								X	X [4]
12-Lead ECG	X		X [9]	X [9]	X [9]	X [9]	X [9]			X [9]	X [9]			X [9]	X [9]		X [9]	X	X [4]

Study Procedures [1]	Screening [2]	Treatment Period (Days)																EOS/ET
		-1 [3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Vital signs	X		X [10]	X [10]	X [10]	X [10]	X [10]			X [10]	X [10]			X [10]	X [10]		X [10]	X	X [4]
C-SSRS [11]	X	X								X							X		X [4]
Sedation VAS			X [12]	X [13]		X [13]				X [13]				X [13]			X [12]	X	X [4]
Pulse oximetry [14]			X														X		
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [4]
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [4]
INDV-2000 dosing [15]				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Midazolam dosing			X														X		
PK Sampling [16]			X	X						X		X					X	X	

AE=adverse event; C-SSRS=Columbia suicide severity rating scale; COVID-19=Coronavirus disease 2019; ECG=electrocardiogram; ET=early termination; EOS=End of study; FSH=follicle stimulating hormone; HIV=Human immunodeficiency; PK=pharmacokinetic; PMP=postmenoposal; VAS=Visual Analogue Scale;

1. For details on Procedures, refer to Section 8.
2. Within 28 days before Day 1 dosing.
3. Participants will be admitted to the study site on Day -1, at the time indicated by the study site, and will remain confined until after the 24-hour blood draw and/or study procedures on Day 16. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per study site requirements.
4. Participants who received all doses of study drugs will return to the study site 7±2 days after the last dose for EOS procedures, and to determine if any AE has occurred since the last study visit. Participants who terminate the study early will be asked to complete EOS procedures at the time of early termination in place of an EOS visit. Participants will be encouraged to stay up to 24 hours after the last dose to complete early termination assessments.
5. Height collected at screening only.

6. For male participants, a testicular/epididymal examination will be performed at screening, on Day 16, and at EOS Visit (7±2 days following last dosing) or early termination. Any clinically significant change from screening will be reported as an AE.
7. Samples for serum chemistry will be obtained after a fast of at least 12 hours, however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.
8. To be performed prior to morning dosing.
9. On Days 1, 2, 4, 8, 12, and 15, 12-lead ECG will be collected within 2 hours prior to morning dose (predose) and at 1 hour (±20 min), 2 hours (±20 min), and 4 hours (±20 min) post morning dose; on Days 3, 5, 9, and 13, 12-lead ECG will be collected within 2 hours prior to morning dose (predose); on Day 16, the 12-lead ECG will be collected at 24 hours post Day 15 morning dose (±20 min).
10. On Days 1, 2, 4, 8, 12, and 15, vital signs will be collected within 2 hours prior to morning dose (predose) and at 1 hour (±15 min), 2 hours (±15 min), and 4 hours (±15 min) post morning dose; on Days 3, 5, 9, and 13, vital signs will be collected within 2 hours prior to morning dose (predose); on Day 16, the vital signs will be collected at 24 hours post Day 15 morning dose (±20 min).
11. Baseline/Screening C-SSRS version (lifetime history and past 6 months) will be completed at screening, the Since last Visit C-SSRS version will be completed at all other time points. On Day 8 and Day 15, C-SSRS will be collected at 6 hours (±1 hour) post morning dose.
12. Sedation VAS will be collected within 1 hour prior to morning dosing (predose) and at 30 min (±5 min), 1 hour (±10 min) and 2 hours (±10 min) post morning dose.
13. Sedation VAS will be collected within 1 hour prior to morning dosing (predose) and at 2 hours (±10 min) post morning dose.
14. Baseline pulse oximetry will be performed within 1 hour prior to morning dosing; pulse oximetry will be monitored continuously with a pulse oximeter for approximately 6 hours post-dose, with readings recorded 2 hours, 4 hours, and 6 hours post-dose (±10 min).
15. INDV-2000 will be administered BID (ie, approximately every 12 hours).
16. For PK collection time points, please refer to Section 10.6 (appendix).

2 INTRODUCTION

INDV-2000 (also referred to as C4X_3256) is a highly potent and selective OX1R antagonist that is being developed as a therapy for the treatment of OUD.

2.1 Study Rationale

2.2 Background

2.2.1 INDV-2000

INDV-2000 is a potent and competitive antagonist of the human OX1R with good selectivity in vitro. In humans, the OX1R is expressed in the brain, predominantly in projections from the lateral hypothalamus, including the ventral tegmental area and the ventromedial prefrontal cortex and it binds the neuropeptide Orexin-A and, with less affinity, Orexin-B. The number of Orexin-A producing neurons is increased in the brains of individuals with heroin dependence (Thannickal 2018). Antagonism of the OX1R inhibits addiction-related behaviours in nonclinical rodent models including self-administration, relapse to drug seeking, and withdrawal (Azizi 2010, Mahler 2012, Hooshmand 2017, Dunn 2019). Hence it is hypothesised that OX1R antagonists should show clinical benefit in the treatment of substance use disorders, including OUD, by reducing craving, relapse, and symptoms of withdrawal.

There are several selective OX1R antagonists (eg, ACT-539313, JNJ-61393215, AZD4041) and dual OX1R/OX2R antagonists already in clinical development. BELSOMRA® (suvorexant) and DAYVIGO® (lemborexant) are dual OX1R/OX2R antagonists approved for the treatment of insomnia (Coleman 2017, Murphy 2017). There have been no published reports of any significant safety issues in animals or humans with these compounds.

The most relevant data on INDV-2000 for the present study are summarised below. A detailed description of the chemistry, pharmacology, efficacy, and safety of INDV-2000 is provided in the most recent Investigator's Brochure (IB) and IB supplement.

Nonclinical summary

[redacted]

Clinical summary

A first-in-human study (INDV-2000-101) to investigate the safety, tolerability and PK of single doses of INDV-2000 has been completed. Through to 01-Nov-2021, 56 healthy volunteers have been administered INDV-2000 as single-dose [redacted]

Additional information on PK and safety of INDV-2000 is provided in the most recent IB and IB supplement.

2.2.2 Midazolam

Midazolam hydrochloride (HCl) is a short-acting benzodiazepine CNS depressant that has sedative, anxiolytic, amnesic, and hypnotic effects.

Oral midazolam is absorbed rapidly from the gastrointestinal (GI) tract and undergoes extensive intestinal and hepatic first pass metabolism. Time to onset of effect is most frequently reported as 10 to 20 minutes and mean T_{max} values ranging from 0.17 to 2.65 hours in paediatric patients. The absolute bioavailability of the midazolam HCl syrup in paediatric patients is about 36%, which is not affected by paediatric age or weight. Midazolam exhibits linear PK between

oral doses of 0.25 to 1 mg/kg. Midazolam is primarily metabolised in the gut and liver by CYP3A4 to its pharmacologic active metabolite, 1-hydroxymidazolam, followed by glucuronidation. The active metabolite, 1-hydroxymidazolam, is equipotent and equally effective as unchanged midazolam on a total plasma concentration basis. Midazolam is also metabolised to 2 other minor metabolites (about 4% of the dose). The mean elimination $T_{1/2}$ of midazolam ranges from 2.2 to 6.8 hours. After oral or intravenous (IV) administration, 63% to 80% of midazolam is recovered in urine as 1-hydroxymidazolam glucuronide.

The most frequently reported AEs following midazolam administration include emesis (8%) and nausea (4%). Midazolam HCl syrup has also been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, most often when used concomitantly with other CNS depressants.

Refer to the full prescribing information for a more detailed background on midazolam (Midazolam HCl Syrup, 2021).

2.3 Benefit/Risk Assessment

Benefit and risk assessment are highlighted below; however more detailed information about the known and expected benefits and risks and reasonably expected AEs of INDV-2000 and midazolam may be found in the IB and IB supplement and in the prescribing information (Midazolam HCl Syrup, 2021), respectively.

2.3.1 Risk Assessment

Investigational Study Drug:

[redacted]

Study Procedures:

A potential risk associated with study procedures are the risks associated with phlebotomy since multiple blood samples are collected throughout the study period. However, limits for number of samples and sample volumes are in place, according to local guidance.

Other Study Medication (Midazolam):

Midazolam is associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, although most often when used concomitantly with other CNS depressants. An oral dose of midazolam (0.1 mg/kg) affects peak saccadic velocity of eye movement, postural sway area, critical flicker fusion frequency, and mental sedation as measured on a VAS (Misaka 2011). To minimise the risk of AE occurrence, a lower dose (5 mg) than that typically required for effective sedation (0.5 mg/kg to a maximum dose of 20 mg) according to the dosing recommendations found in the full prescribing information for midazolam will be administered to ensure a safety margin while allowing robust PK assessment. In addition, as both study drugs may induce somnolence, mental sedation as measured on a VAS will be evaluated throughout the study. Also, oxygen level (oxygen saturation) in the blood will be measured via pulse oximetry in every participants for the 6 hours following each midazolam dosing.

Rescue medication will also be available as needed.

2.3.2 Benefit Assessment

Participants in this clinical study will not receive direct health benefits from study drug during participation. An indirect health benefit to the participants enrolled in this study is the free medical tests received at screening and during the study.

2.3.3 Overall Benefit-risk Conclusion

This is a study in healthy participants, and there is no direct benefit to study participants. The data obtained from this healthy participant study may inform future clinical studies in participants with OUD or other indications under study.

Administration [redacted] BID for 14 days is not expected to cause any safety concern in healthy participants. The dose of midazolam administered in this study is also not anticipated to induce any potential risk to participants taking part in this study, as it is a single dose administered at a lower dose than typically required for effective sedation according to the dosing recommendations found in the full prescribing information for midazolam.

The study site will follow coronavirus plan to minimise the exposure of participants to coronavirus disease 2019 (COVID-19). The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved COVID-19 clinical pharmacology unit management plan will be provided separately.

The safety monitoring practices employed by this protocol (ie, AEs, clinical laboratory tests, vital sign measurements, pulse oximetry, 12-lead ECG, sedation VAS, C-SSRS, and physical examination) are adequate to protect the participants' safety and should detect all expected TEAEs.

3 OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To determine changes in primary PK parameters (maximal and overall plasma exposure) of midazolam and 1-hydroxymidazolam following repeated oral doses of INDV-2000	• C_{max}, $AUC_{0-\infty}$, and AUC_{last} of midazolam and 1-hydroxymidazolam following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
Secondary	
• To assess the safety and tolerability of repeated oral doses of INDV-2000 alone and in combination with midazolam as determined by AE reporting	• Safety and tolerability of INDV-2000 as determined by AE reporting (incidence, seriousness, severity, and relatedness of TEAEs)
Tertiary/Exploratory	
[redacted]	

4 STUDY DESIGN

4.1 Overall Design

- This is an open label, single-centre, fixed-sequence study in healthy adult participants.
- Approximately 20 males and females of non-child bearing potential participants will be enrolled to provide at least 16 evaluable participants.
- The total planned study duration (screening to EOS) for each participant is approximately 7 weeks. This includes a screening period, a treatment period, and an EOS visit:
  - Screening: Day -28 up to dosing on Day 1;
  - Treatment Period: Day 1 to Day 16
    - Day -1: Check-in at the time indicated by the study site, for eligible participants. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per study site requirements.
    - Day 1: Participants will receive a single oral dose of midazolam.
    - Days 2 to 15: Participants will receive oral doses of INDV-2000 BID.
    - Day 15: Participants will receive a single oral dose of midazolam co-administered with INDV-2000 morning dose.
    - Day 16: Check-out from the study site following completion of the 24-hour blood draw and/or study procedures scheduled on that day; note that the study site may decide to confine the participants for longer periods at the Investigator's discretion.
  - EOS Visit: Participants who received all doses of study drugs will return to the study site 7±2 days after the last dose for EOS procedures, and to determine if any AE has occurred since the last study visit. Participants who terminate the study early will be asked to complete EOS procedures at the time of early termination in place of an EOS visit and will be encouraged to stay up to 24 hours after the last dose to complete early termination assessments.
- Blood sampling for midazolam and 1-hydroxymidazolam plasma concentrations will be conducted for 24 hours on Day 1 and Day 15.

[redacted]

- Safety will be monitored throughout the study by AE review, clinical laboratory tests, vital sign measurements, pulse oximetry, ECG parameters, C-SSRS, sedation VAS, and physical examination.

4.2 Scientific Rationale for Study Design

This clinical study will evaluate the potential effect of INDV-2000 on the activity of CYP3A, thereby providing information on whether CYP3A substrate drugs can be co-administered safely with INDV-2000, and if there is a need for focused clinical DDI studies (eg, oral contraceptive studies). Midazolam is considered a sensitive index substrate of CYP3A4 as per the Food and Drug Administration's (FDA's) web site for Drug Development and Drug Interactions (FDA 2022) and was thus selected as a probe for this study. Although the syrup formulation is indicated for use in paediatric patients, it was selected over the IV formulation as it allows to assess the intestinal CYP3A activity and is routinely used in the adult population and commonly selected for DDI studies.

The study is designed as an open label, fixed-sequence study for the following reasons:

- Since the primary endpoint is an objective measurement, there is no risk of potential bias of the study results; hence, neither study blinding nor inclusion of a placebo group is required, and the study can be conducted as open label.
- A fixed-sequence allows to prevent any carryover effect of INDV-2000 on CYP3A activity due to INDV-2000 potential inductive effect while providing the advantage of reducing the study variability since participants act as their own control.

Since the purpose of the study is to validate the potential of INDV-2000 to perpetrate induction, and as it may take about 2 weeks of daily administration to achieve maximum level of induction for a perpetrator, INDV-2000 will be administered for 14 days (Day 2 to Day 15) with the substrate being co-administered on Day 15.

Oral administration of midazolam has demonstrated linear PK and thus will be given as a single dose.

Based on the short half-life of midazolam and 1-hydroxymidazolam, PK sampling for a duration of 24 hours should be adequate to ensure robust characterization of total exposure of the analytes. Blood samples for INDV-2000 will be collected to confirm expected plasma concentrations.

4.3 Justification for Dose

[redacted]

4.4 End of Study Definition

The end of the study is defined as the EOS visit (Day 22±2 days).

A participant is considered to have completed the study if the participant has completed dosing, did not discontinue or terminate the study early, and has completed most of the scheduled procedures including the EOS visit (Day 22±2 day).

4.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH/GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study-site staff. It is the responsibility of the Investigator and study-site staff to use continuous vigilance to identify and report deviations to Indivior or specified designee, and to the IRB/IEC per local requirements.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
2. Body weight of a minimum of 50.0 kg at the Screening Visit and body mass index within the range 18.0 – 32.0 kg/m^2 (inclusive).
3. Male or female who is healthy as determined by medical evaluation.
4. Females will be of non-childbearing potential. Females of non-childbearing potential are considered women who:
   - Do not have a uterus, or
   - Are surgically sterile (eg, has undergone complete hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, or tubal ligation), or
   - Have permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries, or
   - Are post-menopausal as defined by 12 months or more of spontaneous amenorrhea as confirmed by a follicle-stimulating hormone (FSH) >30 mIU/mL
5. Male participants agree to follow contraception guidelines in Section 10.3 (appendix).
6. Continuous non-smoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to the first dosing based on participant self-reporting.
7. Capable of giving signed informed consent as described in Section 10.1.3 (appendix) which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Have an ongoing medical history of clinically significant neurological, cardiovascular, renal, hepatic, chronic respiratory or GI disease, psychiatric or other disorder as judged by an Investigator that could potentially affect the study outcomes or compromise participant safety.
2. Have clinically significant abnormal biochemistry, haematology or urinalysis results as judged by an Investigator.
3. Have a history of narcolepsy or sleep apnea.
4. Have disorders that may interfere with drug absorption, distribution, metabolism and excretion processes.

5. Current active hepatic or biliary disease.
6. Participants with cholecystectomy <90 days prior to screening.
7. Positive test results for human immunodeficiency virus (HIV)-1/HIV-2 antibodies, Hepatitis B surface antigen (HBsAg) or Hepatitis C antibodies.
8. Have a blood pressure reading outside of the following range: Systolic <86 or >149 mmHg; Diastolic <50 or >94 mmHg
9. Serious cardiac illness or other medical condition including, but not limited to:
    - Uncontrolled arrhythmias
    - History of congestive heart failure
    - QTcF >450 msec for males and >470 msec for females or history of prolonged QT syndrome
    - Myocardial infarction
    - Uncontrolled symptomatic angina
10. History of suicidal ideation within 30 days prior to providing written informed consent as evidenced by answering "yes' to questions 4 or 5 on the suicidal ideation portion of the C-SSRS completed at the Screening Visit or history of a suicide attempt (per the C-SSRS) in the 6 months prior to informed consent.
11. Healthy participants who are taking, or have taken, any prescribed or over-the-counter drugs (other than 2 grams of acetaminophen per 24-hour period as of Day 1, hormone replacement therapy, or thyroid hormone replacement therapy [see Section 6.9]) or herbal remedies in the 14 days or 5 half-lives (whichever is longer) prior to first dose of study drug.
12. Treatment with any known drugs that are moderate or strong inhibitors/inducers of CYP3A4 or CYP2C19, including St. John’s Wort, within 30 days prior to first dose of study drug.
13. Any consumption of food or drink containing poppy seeds, grapefruit or Seville oranges within 14 days prior to the first dose of study drug.
14. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine).
15. Positive test result for alcohol and/or drugs of abuse at screening or at check-in.
16. Female participant with a positive pregnancy test at the Screening Visit or at first check-in or who are lactating.
17. Concurrent treatment or treatment with an investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug.
18. Blood donation of approximately 500 mL or more within 56 days or plasma donation within 7 days of screening.
19. Known hypersensitivity to INDV-2000 or any other ingredient in the INDV-2000 formulation.

20. Known hypersensitivity to midazolam or any other ingredient in midazolam HCl syrup.
21. Site staff and/or participants who have a financial interest in, or an immediate family member of either the site staff and/or Indivior employees, directly involved in the study.
22. Major surgical procedure (as defined by the Investigator) within 90 days prior to the first dose of study drug or still recovering from prior surgery.
23. Concurrent enrolment in another clinical study, unless it is an observational study.
24. Participants who are unable, in the opinion of the Investigator, to comply fully with the study requirements.
25. Any condition that, in the opinion of the Investigator or Indivior, would interfere with evaluation of the study drug or interpretation of participant safety or study results.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1. No water (except water provided with dosing) is allowed from 1 hour prior to and until 1 hour after each dosing of study drug, but will be allowed ad libitum at all other times.
2. On all PK days (Day 1 and Day 15), participants will fast overnight for at least 10 hours before and at least 4 hours after each morning dose of study drug. For all other dosing, participants will fast for at least 2 hour before and at least 2 hours after dosing of study drug.
3. On all days that participants are confined in the study site, meals and/or snacks will be provided at appropriate times. Each meal and/or snack served at the study site will be standardised and will be similar in caloric content and composition. Participants will not be required to fully consume any meal or snack.
4. Refrain from consumption of food or drink containing poppy seeds, grapefruit or Seville oranges from 14 days before the first dosing of study drug until after collection of the final PK sample.
5. Participants should be instructed to fast for at least 12 hours before collection of fasting clinical laboratory assessment samples as indicated in Section 10.2 (appendix).

5.3.2 Caffeine, Alcohol, and Tobacco

1. Participants will be instructed to abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours prior to the first dose of study drug until after collection of the final PK sample.

   Small amounts of caffeine derived from normal foodstuffs (eg, 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of

espresso; 45 g/1.5 oz chocolate bar per day) would not be considered a deviation to this restriction.

2. Participants will be instructed to abstain from alcohol for 48 hours prior to the first dose of study drug until after collection of the final PK sample.
3. Participant will abstain from use of nicotine- or tobacco-products from 3 months before the first dosing and through confinement.

5.3.3 Activity

1. Participants will remain seated for the first 4 hours post morning dose and the first 2 hours post evening dose, except when they are supine or semi reclined for study procedures. Participants will then resume normal activity. During the first 4 hours post morning dose or 2 hours post evening dose, participants may be allowed to rise for brief periods under supervision (eg, in order to use the toilet facilities).
2. Should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.
3. Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from the Screening Visit until completion of the study.

5.4 Screen Failures

See Section 9.2 for definition of enrolled participant.

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, reason for screen failure, such as not eligible, withdrew consent, AE), eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the medical monitor.

5.5 Early Discontinuation

A participant will be considered an early discontinuer if the participant received study drug and did not complete all visits. Reasons for not completing all visits will be captured in the participant source documents and the Case Report Form (CRF).

The definition of a study completer is provided in Section 4.4.

6 STUDY DRUG AND CONCOMITANT THERAPY

Study drug is defined as any investigational drug(s), marketed product(s), placebo or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Drug(s) Administered

Table 2 Study Drugs Administered

Drug Name	INDV-2000	Midazolam HCl
[redacted]		

6.2 Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug as per the pharmacy manual.
2. Only participants enrolled in the study may receive study drug and only authorised site staff may supply or administer study drug. The dispensing of study drug to the participant must be documented on the drug dispensing form. All study drug dispensation will be performed by a pharmacist or designee, checked by a study centre staff member and documented on a drug dispensation form. Refer to the pharmacy manual for further details.
3. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Participant level dispensation of study drug must be documented on the appropriate participant level accountability form. All study drug dispensation will be performed by a pharmacist or designee, checked by a study-site staff member and documented on a drug dispensation form.
6. Used and unused study drug must be available for verification by the site monitor during on-site monitoring visits.
7. Further guidance and information for the final disposition of unused study drugs are provided in the pharmacy manual.
8. Upon completion of the study and/or as requested by Indivior, copies of study drug accountability records will be provided to Indivior or designee.

6.2.1 Drug Administration

When participants are dosed at the site, they will receive the study drug(s) directly from the Investigator or designee, under medical supervision.

A record of the number of INDV-2000 capsules dispensed to and taken by each participant must be maintained and reconciled with study drug and compliance records. Study drug administration date and time will be recorded in the CRF (See Section 6.5).

Treatment is as follows:

- Midazolam 5 mg (2.5 mL of 2 mg/mL syrup) on Day 1
- INDV-2000 [redacted] BID on Day 2 to Day 15 with midazolam 5 mg (2.5 mL of 2 mg/mL syrup) co-administered on the morning of Day 15

- Following initial INDV-2000 morning dosing on Day 2, each subsequent INDV-2000 morning dose will be administered within 1 hour before or after the dosing time established on Day 2. For each evening dose, INDV-2000 will be administered approximately 12 hours after the morning dose on that day.
- The pharmacy at the study site will provide each dose in individual unit dose containers for each participant, as appropriate. When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.
- Study drugs will be administered under fasted conditions with approximately 240 mL of water (see Section 5.3.1).
- Participants will be instructed not to crush, split, or chew the capsules.
- The exact clock time of dosing will be recorded.
- Dosing compliance will be monitored as described in Section 6.5.

6.2.2 Reporting Product Complaints

The Investigator and study-site staff are responsible for prompt recognition and reporting of product quality complaints to Indivior [redacted] **within 1 business day of identifying the issue**.

A product complaint is any concern pertaining to the manufacturing or quality control of the study drug and includes, but is not limited to broken capsules, labelling defects, packaging defects, or study drug that is thought to be ineffective, or has an appearance, taste, or odour that is outside of what is expected.

See the pharmacy manual for further details.

The following information should be provided:

- study number
- site contact/reported by
- participant number (if already assigned to a participant)
- description of issue
- picture, if available (photographs should be taken only if safe to do so/within site policy or practice to take photograph)

Retain the product and packaging in quarantine for further investigation, as required.

6.3 Assignment to Study Intervention

The Investigator is responsible for maintaining a master list (ie, a participant identification list) of all consented participants and will document all participants that did not meet study eligibility criteria (ie, screen failures), including reason(s) for ineligibility (ie, a participant screening and enrolment log).

Each participant will be assigned a unique identification number upon the Screening Visit. Participants who complete the study screening assessments and meet all the eligibility criteria

will be assigned a unique identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product.

All participants will receive each treatment in a sequential manner.

6.4 Blinding/Masking

This is an open label study. There is no randomization in this study.

6.5 Study Drug Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. The date and time of each dose administered will be recorded in the source documents and recorded in the CRF. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drug. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth. Participants' hands will also be verified to ensure that the study drug was ingested.

Any deviation(s) from the prescribed dosage regimen will be recorded in the electronic (e)CRF.

The time of dosing is defined as the time the participant has swallowed the study drug and the qualified designee has completed check of oral cavity and hands.

The exact clock time of dosing will be recorded.

6.6 Dose Modification

The dose and administration of the study drugs to any participant may not be modified.

6.7 Treatment Access to Study Drug After the End of the Study

Not applicable.

6.8 Treatment of Study Drug Overdose

For this study, any dose of study drug greater than that specified in the protocol will be considered an overdose. In the event of overdose, general supportive measures and close monitoring are recommended.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose, the Investigator should do the following:

1. Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study drug should be interrupted or whether the dose should be reduced.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample (for INDV-2000 or midazolam and 1-hydroxymidazolam) for PK analysis within 24 hours from the time of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any medication (including prescription and non prescription medications, vitamins and dietary or herbal supplements) that the participant is receiving during the study must be recorded along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must not have received concurrent treatment or treatment with investigational drug or device within 5 half-lives (if known) of the investigational agent or 30 days prior to the first dose of study drug, whichever is longer.

Participants must abstain from taking any prescribed or over-the-counter drugs or herbal remedies within 14 days or 5 half-lives (whichever is longer) prior to first dose of study drug until completion of the 7±2 days EOS Visit. Hormone replacement therapy and thyroid hormone replacement therapy, if the participant has been on the same stable dose for at least 3 months prior to the first dosing, will also be allowed. After first dosing of study drug, acetaminophen, at doses of up to 2 grams/24 hours, is permitted for use at the discretion of the Investigator or designee.

Moderate or strong inhibitors/inducers of CYP3A4 or CYP2C19, including St. John's Wort, will be prohibited within 30 days prior to first dose of study drug until completion of the 7±2 days EOS Visit. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with the study drug(s).

6.9.1 Rescue Medicine

For severe AEs, including any midazolam-related events such as respiratory depression and oxygen desaturation, standard contents of the emergency crash cart available at the study site (eg, oxygen, flumazenil) will be used as rescue medication at the discretion of the Investigator or designee.

7 DISCONTINUATION OF STUDY DRUG, PARTICIPANT DISCONTINUATION/WITHDRAWAL AND STOPPING CRITERIA

7.1 Discontinuation of Study Drug and Study Stopping Criteria

[redacted]

7.1.1 Liver Chemistry Stopping Criteria

[redacted]

7.1.2 QTc Stopping Criteria

[redacted]

[redacted]

7.3 Lost to Follow-up

An enrolled participant who has received study drug will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 2 contact attempts (eg, telephone calls and/or emails and, if necessary a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoE (Section 1.3); individual clinical procedures are described in detail below.
- Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The blood collections for midazolam and 1-hydroxymidazolam are the critical parameters and need to be done as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.
- Repeat or unscheduled samples may be obtained for safety reasons.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by Indivior or the Investigator, as per local health authority/ethics requirements.

Table 3 Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including haematology, serum chemistry, serology, and coagulation), FSH (for PMP female participants only) and serum pregnancy (for female participants only).	1	16	16
On-study haematology, serum chemistry	8	12.5	100
On-study coagulation (prothrombin time/International normalised ratio [INR] and activated partial thromboplastin time)	4	3.5	14
Blood for Midazolam and 1-hydroxymidazolam PK	32	4	128
[redacted]			
		Total Blood Volume (mL)→	294 **

* Represents the largest collection tube that is expected to be used (a smaller tube may be used).

** If additional safety or PK analysis are necessary, additional blood may be obtained (up to a maximum of 50 mL).

8.1 Administrative Procedures

8.1.1 Informed Consent Procedure

Refer to Section 10.1.3.

8.1.2 Inclusion and Exclusion Criteria

Refer to Section 5.1 and Section 5.2.

8.1.3 Medical History/Demography

At screening, medical history and demographic data, including name, sex, age, race, ethnicity, psychiatric history, and substance use will be recorded.

8.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 6.9. All medications taken by participants during the course of the study will be recorded.

8.1.5 Check-in Criteria

Upon passing screening and meeting inclusion and not meeting exclusion criteria, the participant will be admitted to the study site on Day -1. Once admitted, participants must meet the following criteria prior to Day 1 dosing:

- A check-in questionnaire will be reviewed for each participant to ensure that participants remain eligible for the study since screening. Questions will focus on inclusion and exclusion criteria and on study restrictions.
- Female participants must have a negative urine pregnancy test.
- Participants must have a negative result obtained from the urine drug screen and the alcohol test.
- Participants must have a negative polymerase chain reaction test result for COVID-19.

If any of these criteria are not met, the participant will not be enrolled.

8.2 Efficacy and/or Immunogenicity Assessments

Efficacy and/or immunogenicity are not evaluated in this study.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoE (Section 1.3). Individual clinical procedures are described in detail below.

Additional safety assessments may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

8.3.1 Physical Examinations

- Physical examination will be conducted as outlined in the SoE (Section 1.3).
- Male participants will undergo a testicular exam as outlined in the SoE (Section 1.3).

- Additional physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.
- A complete physical examination will include, at a minimum, an examination of all major body/organ systems (including skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities). Height and weight (with participants wearing indoor, daytime clothing with no shoes) will also be measured and recorded as outlined in the SoE (Section 1.3).

8.3.2 Vital Signs

- Single vital signs will include the collection of oral body temperature, respiratory rate, blood pressure, and pulse rate and will be conducted as outlined in the SoE (Section 1.3).
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate will be assessed with the participant resting in a seated position for at least 5 minutes, except when participants are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.
- When scheduled pre-dose, vital signs will be measured within 2 hours prior to morning dosing for the pre-dose morning time points. When scheduled post-dose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

8.3.3 Electrocardiograms

- Single 12-lead ECG will be conducted as outlined in the SoE (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- ECGs will be performed with participants resting in a supine position for at least 5 minutes. All ECG tracings will be reviewed by the Investigator or designee.
- When scheduled pre-dose, ECGs will be measured within 2 hours prior to morning dosing. When scheduled post-dose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

8.3.4 Pulse Oxymetry

- Pulse oximetry reading will be collected using a pulse oximeter (oxygen levels as saturation [%]) as outlined in the SoE (Section 1.3).
- Where the time of reading coincides with a blood sampling time point, the reading will be collected within approximately 10 minutes prior to the scheduled time point. Readings may be taken at other times, if deemed necessary by the Investigator or designee.
- Any oxygen saturation reading deemed clinically significant by the Investigator will be documented as an AE.

8.3.5 Clinical Safety Laboratory Tests

- See Section 10.2 (appendix) for the list of clinical laboratory tests to be performed and to the SoE (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review and record any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and Indivior notified.
    - All protocol-required laboratory tests, as defined in Section 10.2 (appendix), must be conducted in accordance with the laboratory manual and the SoE (Section 1.3).
    - If laboratory values from non–protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.
    - Serum chemistry tests will be performed after at least an 12-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.

8.3.6 Pregnancy Testing

- Pregnancy testing will be conducted at as outlined in the SoE (Section 1.3).
- In the case where a participant's routine pregnancy test as required per protocol is positive for pregnancy prior to dosing, the participant should not be dosed. If the participant has a positive urine pregnancy test, a confirmatory serum pregnancy test should be performed.
- Additional pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.3.7 Suicidal Ideation and Behaviour Risk Monitoring

- The C-SSRS is a questionnaire scale to detect emergent suicide symptoms (suicidal ideation or actual suicidal behaviour). Baseline evaluations will assess the lifetime experience of the participant with suicidal ideation and behaviour and post baseline evaluations will focus on suicidality since the last study visit.
- C-SSRS questionnaire will be conducted as outlined in the SoE (Section 1.3); the Baseline/Screening C-SSRS version will be completed at screening (lifetime history and

past 6 months) and the Since Last Visit C-SSRS version will be completed at all other time points.

- On Day 8 and Day 15, C-SSRS will be conducted within 1 hour of the scheduled time point.
- Additional C-SSRS assessment may be performed at other times if deemed necessary by the Investigator or designee.
- The C-SSRS is to be administered at the site by an appropriately qualified/trained individual and a copy of the questionnaire to be used will be kept in the study binder. In addition, participants who at any time during this study spontaneously report AEs of suicidal ideation or suicidal behaviour must be assessed by the Investigator or designee and referred for further mental health evaluation as clinically indicated.

8.3.8 Sedation VAS

- VAS will be conducted as outlined in the SoE (Section 1.3)
- When scheduled pre-dose, VAS will be measured within 1 hour prior to morning dosing. When scheduled post-dose, VAS will be performed within approximately 5 minutes for the 30-minute scheduled time point and within 10 minutes for the 1-hour and 2-hour scheduled time points.
- The VAS to be used will be provided in a separate document.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided below, as are criteria for assessment of AE/SAE intensity and causality.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures or that caused the participant to discontinue the study drug (see Section 7).

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from screening (signing of the ICF), considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before signing the ICF.
- Signs, symptoms, or the clinical sequelae of a suspected DDI or that resulted in additional intervention (eg, concomitant medication, surgery).
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events not meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety findings that are not considered to be clinically significant by the Investigator.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, hospitalisation for elective surgery, hospitalisation for observation in the absence of an AE).

Definition of SAE

An SAE is defined as any untoward medical occurrence that:

a. Results in death

b. Is life-threatening

The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation signifies that the participant requires inpatient HOSPITALISATION or prolongation of existing hospitalisation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether “hospitalisation” occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from screening (signing of the ICF) is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza,

and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of study drug dependency or study drug abuse.
- An SAE must be reported for participants with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct).

Definition of SUSAR

A suspected unexpected serious adverse reaction (SUSAR) is an SAE with at least a reasonable possibility of being related to the study drug (ie, the relationship cannot be ruled out), the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Assessment of Intensity

The Investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Toxicitiy

Separately, the toxicity of AEs will be graded in accordance with the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Section 10.7). Any event not falling under one of the specific categories listed will be graded as a “Systemic Illness”.

For events that occur after first study drug administration, the maximum intensity, toxicity, and seriousness should be reflected in the event record.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The relationship of each AE to study drug will be assessed using the following categories:
  - **Related**: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
  - **Not Related**: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Indivior. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Indivior.
- The Investigator may change opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Clinical Laboratory Changes

Changes in laboratory values, vital signs, or other safety parameters (eg, neurological and clinical symptom assessments) as noted in the protocol are a subset of AEs and are reportable only if the laboratory test result is associated with accompanying symptoms, and/or requires additional diagnostic testing or intervention (medical, surgical), and/or requires additional significant treatment, and/or requires temporal or permanent discontinuation of study drug or a change to dosing other than as permitted by protocol, or if considered to be clinically significant by Investigator or medically qualified designee.

Screening laboratory assessments, if determined to be clinically significant by the Investigator, are not AEs.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from ICF signature until the EOS Visit on Day 22 (±2 days) or at early termination. Any ongoing AEs at the time of the EOS Visit (ie, Day 22 [±2 days]) or at early termination will be appropriately followed-up until resolution or 14 days after the EOS Visit or early termination. Any ongoing SAEs will be followed-up until resolution or lost to follow-up.

All SAEs will be recorded and reported to Indivior or designee immediately and under no circumstance should this exceed 24 hours from first becoming aware of the event, as indicated in Section 8.4.3. The Investigator will submit any updated SAE data to Indivior within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify Indivior.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Reporting and Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained or the participant is lost to follow up (as defined in Section 7.3). Further information on follow up procedures is provided in Section 8.4.3.2.

Once the Investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Indivior (or designated representative) by the Investigator (or designee) within 24 hours from first being aware of the event using the form provided by Indivior or designated representative. Any follow up information on a previously reported SAE will also be reported to Indivior within 24 hours.

Where additional information is needed or expected, the Investigator will not wait to receive all information before reporting the event to Indivior. The Investigator must provide an assessment of causality at the time of the initial report as described in Section 8.4.

8.4.3.1 Reporting of SAEs

SAE Reporting to Indivior via Paper SAE Reporting Form

- The primary mechanism for reporting an SAE to Indivior Pharmacovigilance will be by completing the paper SAE Reporting Form provided by Indivior. Follow-up information will also be reported using the paper SAE Reporting Form.

- The SAE Reporting Form should be completed and submitted to Indivior Pharmacovigilance:

[redacted]

- The site will report all SAEs within 24 hours from first being aware of the event. Any follow-up information on a previously reported SAE will also be reported to Indivior within 24 hours.

8.4.3.2 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Indivior in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by Indivior Pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Indivior Pharmacovigilance.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Indivior Pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Indivior within 24 hours of receipt of the information.
- After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to Indivior of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

- Indivior has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. Indivior will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Indivior will review and then file it along with the IB and/or package insert and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Indivior policy and forwarded to Investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and in female partners of male participants will be collected after the first study drug administration and until 90 days following the last dose.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Indivior within 24 hours of learning of the female participants and in female partners of male participants (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- All pregnancy exposure cases (unless permission has been denied), where the embryo or foetus may have been exposed to study drug (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure) whether associated with an AE or not, will be followed in order to collect information on the outcome of the pregnancy (ie, termination [voluntary or spontaneous] or birth). Make 2 attempts to obtain information after the expected due date, with 1 month between the 2 attempts. If there is no response, the case will be closed.
- Abnormal pregnancy outcomes (eg, foetal death, stillbirth, congenital anomalies, ectopic pregnancy, abortion [except pregnancy in habitual aborter, prophylaxis of abortion], pre-eclampsia, eclampsia) are considered SAEs and will be reported as such.
- The female participants and in female partners of male participants will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the female participants and in female partners of male participants and the neonate and the information will be forwarded to Indivior.
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to Indivior as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former female participants and in female partners of male participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.5 Pharmacokinetics

8.6 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics OR Medical resource utilisation and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There are no formal statistical hypotheses for this study.

The primary objective of the study is to determine changes in primary PK parameters of midazolam and 1-hydroxymidazolam. These changes will be estimated by calculating the geometric mean ratio (GMR) of each primary PK parameter with and without INDV-2000, where "with" is considered the test treatment and "without" is considered the reference. Ninety (90)% confidence intervals for the GMRs will be calculated.

9.1.1 Multiplicity Adjustment

There are no inferential statistics for this study; therefore, multiplicity adjustment is not applicable.

9.2 Analyses Sets

For purposes of analysis, the following populations are defined:

Table 4 Populations for Analysis

Population	Description
Screened	All participants who sign the ICF.
PK Analysis Set	All participants who receive at least one dose of study drug and have an adequate number of PK samples collected to derive any PK parameter, and have no protocol deviations that would significantly alter plasma concentrations of study drugs. All available data will be included in the concentration and PK parameter tables to the extent possible. Data for each participant will be included in the summary statistics and statistical comparisons of PK parameters.
Safety Analysis Set	All participants who receive at least 1 dose of study drug.

9.3 Statistical Analyses

9.3.1 General Considerations

The statistical analysis plan (SAP) will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. The SAP will be prepared by Indivior. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.3.2 Primary Endpoints Analysis

For both midazolam and 1-hydroxymidazolam, C_{max}, $AUC_{0-\infty}$, and AUC_{last} in the presence (Day 15) of INDV-2000 will be compared to C_{max}, $AUC_{0-\infty}$, and AUC_{last}, respectively, in the absence (Day 1) of INDV-2000 using GMRs and 90% CIs calculated using random effects models. The primary endpoints will be analysed using the PK Analysis Set. Details on the statistical analyses will be included in the SAP.

9.3.3 Secondary Endpoints Analysis

TEAEs will be defined as AEs that start on or after the first dose of study drug and will be summarised by Medical Dictionary for Regulatory Activities system organ class and preferred term. TEAEs will be summarised for the Safety Analysis Set.

9.3.4 Tertiary/Exploratory Endpoints Analysis

[redacted]

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

Approximately 20 participants will be assigned to receive study drug. This sample size is based on earlier clinical experience and is expected to provide at least 16 evaluable participants, defined as participants with plasma concentration-time profiles sufficient for calculation of PK parameters during the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before use in the study. If required by local regulations, the protocol should be re-approved by the IRB/IEC annually. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH/GCP.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol may require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide Indivior with sufficient, accurate financial information (when applicable) as requested to allow Indivior to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- Written informed consent must be obtained prior to any study-related.
- The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, if required by the IRB/IEC.
- A copy of the ICF(s) must be provided to the participant.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the study site. Any participant records or datasets that are transferred to Indivior will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by Indivior in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their study records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by Indivior, and by inspectors from regulatory authorities.
- The contract between Indivior and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

10.1.5 Dissemination of Clinical Study Data

This study will be registered on ClinicalTrials.gov, European Clinical Trials Database, or the country's clinical study registry, as appropriate, and in accordance with national, regional, and local regulations. Release of applicable clinical study results will proceed in compliance with local regulations in accordance with the principles of Good Publication Practice.

A clinical study report will be prepared following completion of the study. An Investigator signatory may be identified for the approval of the report if required by applicable regulatory requirements.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or CRFs unless transmitted to Indivior or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be described in the CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- Investigator Site Audits include, but are not limited to, review of drug supply, presence of required documents, the informed consent process, comparison of CRFs with source documents, and any other study-specific information/documentation that the auditor deems appropriate for review during the audit. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to Indivior's or a Contract Research Organization's Quality Assurance SOPs.
- In addition, this study is subject to inspections by regulatory authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the regulatory inspector direct access to all relevant study documents. The Investigator must contact Indivior immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- Indivior or designee is responsible for the data management of this study including quality checking of the data.
- Indivior assumes accountability for actions delegated to other individuals (eg, contract research organisations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator as dictated by ICH/GCP guidelines, as well as in accordance with the site's Standard Operating Procedure requirements and local regulations or institutional policies. No records may be destroyed without the written approval of Indivior. No records may be transferred to another location or party without written notification to Indivior.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- The Investigator is responsible for the quality of the data recorded in the CRFs. The data recorded should be a complete and accurate account of the participant's record collected during the study.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents may be electronic, hard copy, or a combination of both and are defined as the results of original observations and activities of a clinical investigation. When using a direct entry CRF, the CRF will be considered the source document for applicable CRF elements collected directly onto a CRF. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for direct inspection by the authorised study personnel outlined in the ICF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Indivior or designee will perform monitoring to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the time study is published to the call centre and Helpresearch.com website and will be the study start date.

Study/Site Termination

Indivior or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Indivior. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Indivior or Investigator may include but are not limited to the following:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Indivior procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, Indivior shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

The study data will be owned by Indivior. Publication of any and all data will be at the discretion of Indivior. The Investigator will not disseminate, present, or publish any of the study data without the prior written approval from Indivior to do so.

- Indivior will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Indivior will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Female participants should only be enrolled after a negative serum pregnancy test result at screening and a negative urine pregnancy test result at check-in. Additional pregnancy testing will be performed as specified in the SoE (Section 1.3) and as deemed necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

Table 5 Protocol-required Safety Laboratory Tests

Haematology
- Haemoglobin
- Haematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation
- Prothrombin time/INR
- Activated partial thromboplastin

Serum Chemistry *
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase (ALP)
- AST
- ALT
- Gamma-glutamyl Transferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine **
- Total protein
- Total cholesterol
- Triglycerides
- Creatine phosphokinase

Urinalysis
- pH
- Specific gravity
- Protein ***
- Glucose
- Ketones
- Bilirubin
- Blood ***
- Nitrite***
- Urobilinogen
- Leukocyte esterase ***

Additional Tests
- HIV-1; HIV-2 (screening only)
- HBsAg (screening only)
- HCV antibodies (screening only)
- Urine drug screen
  - Opiates §
  - Opioids
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
  - Fentanyl
  - Oxycodone
- Urine alcohol screen
- Serum pregnancy test (for females only; screening only)
- Urine pregnancy test (for females only)
- FSH (for PMP females only; screening only)
- COVID-19 PCR (check-in only)

* Serum chemistry tests will be performed after at least an 12-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.

** At the Screening Visit, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is abnormal for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1 Definitions

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Do not have a uterus, or
- Are surgically sterile (eg, has undergone complete hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, or tubal ligation), or
- Have permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries, or
- Are post-menopausal as defined by 12 months or more of spontaneous amenorrhea as confirmed by a FSH >30 mIH/mL.

10.3.2 Contraception Guidance

Female Participants

No contraception methods are required as females of childbearing potential will not be eligible to enroll in the study. Only females of non-childbearing potential will be enrolled.

Male Participants

Male participants with female partners of childbearing potential must comply with the following contraception requirements from the time of first dose of study medication until at least 90 days after the last dose of study medication.

- All non-sterile male participants must use highly effective contraception from first study drug administration through 90 days after their last study drug administration if sexually active with a non-pregnant partner of child bearing potential. Highly effective contraception is defined as:
    - True sexual abstinence
    - Condom plus partner's use of:
        - Oral, intravaginal, injectables, implants, or transdermal combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
        - Intrauterine device
        - Intrauterine hormone-releasing system
        - Bilateral tubal occlusion
- No restrictions are required for a vasectomised male provided his vasectomy has been performed 4 months or more prior to the first dosing. A male who has been vasectomised less than 4 months prior to the first dosing must follow the same restrictions as a non-vasectomised male.

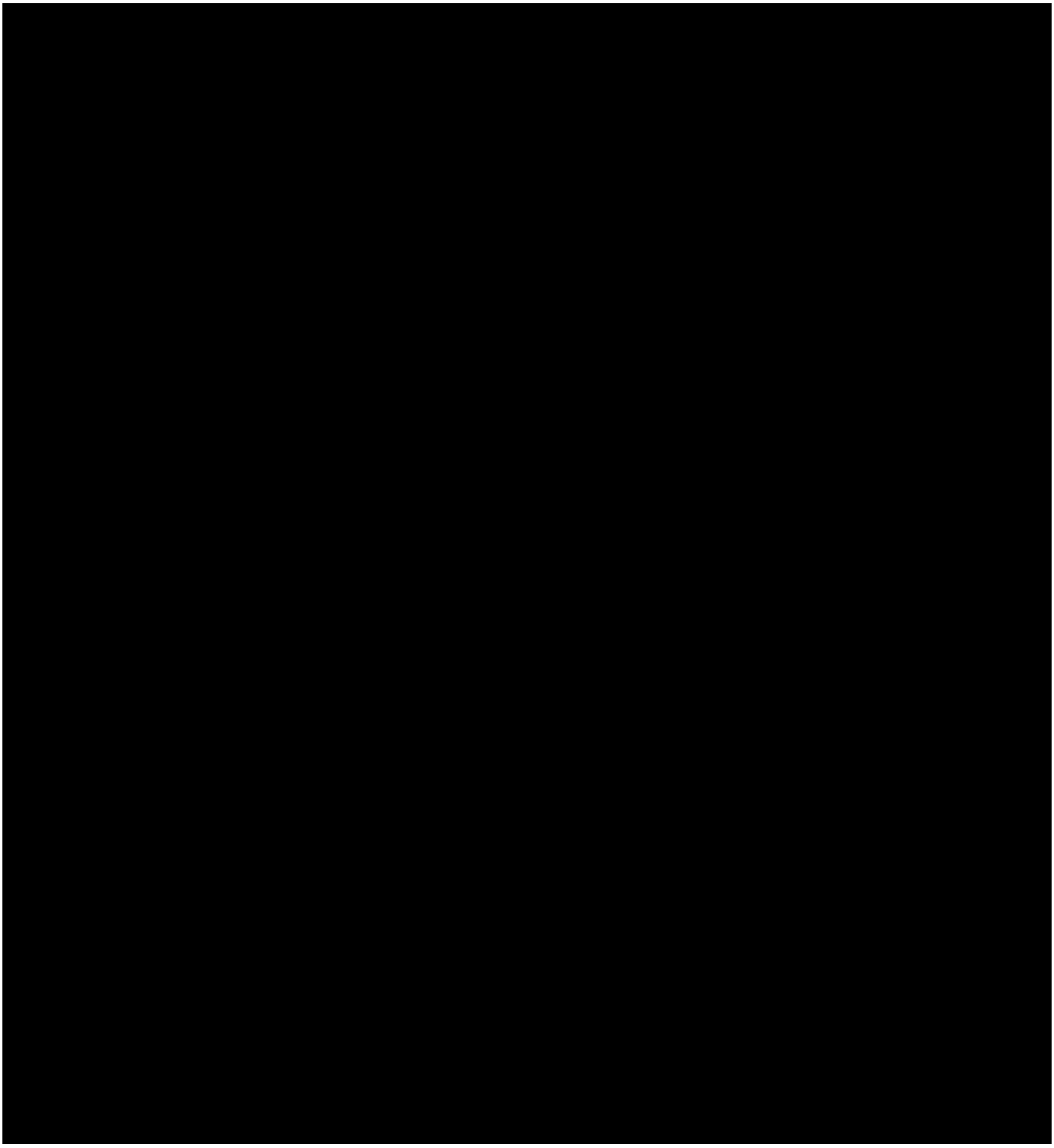
Male participant must agree not to donate sperm from the first dosing until at least 90 days after the last dosing.

10.4 Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

The following should occur if a participant meets any of the liver chemistry stopping criteria as outlined below:

Phase I liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase I Liver Chemistry Stopping Criteria and Follow-Up Assessments



References

EASL Clinical Practice Guidelines: Drug-induced liver injury. J of Hepatol. 2019; 70 (6):1222-61.

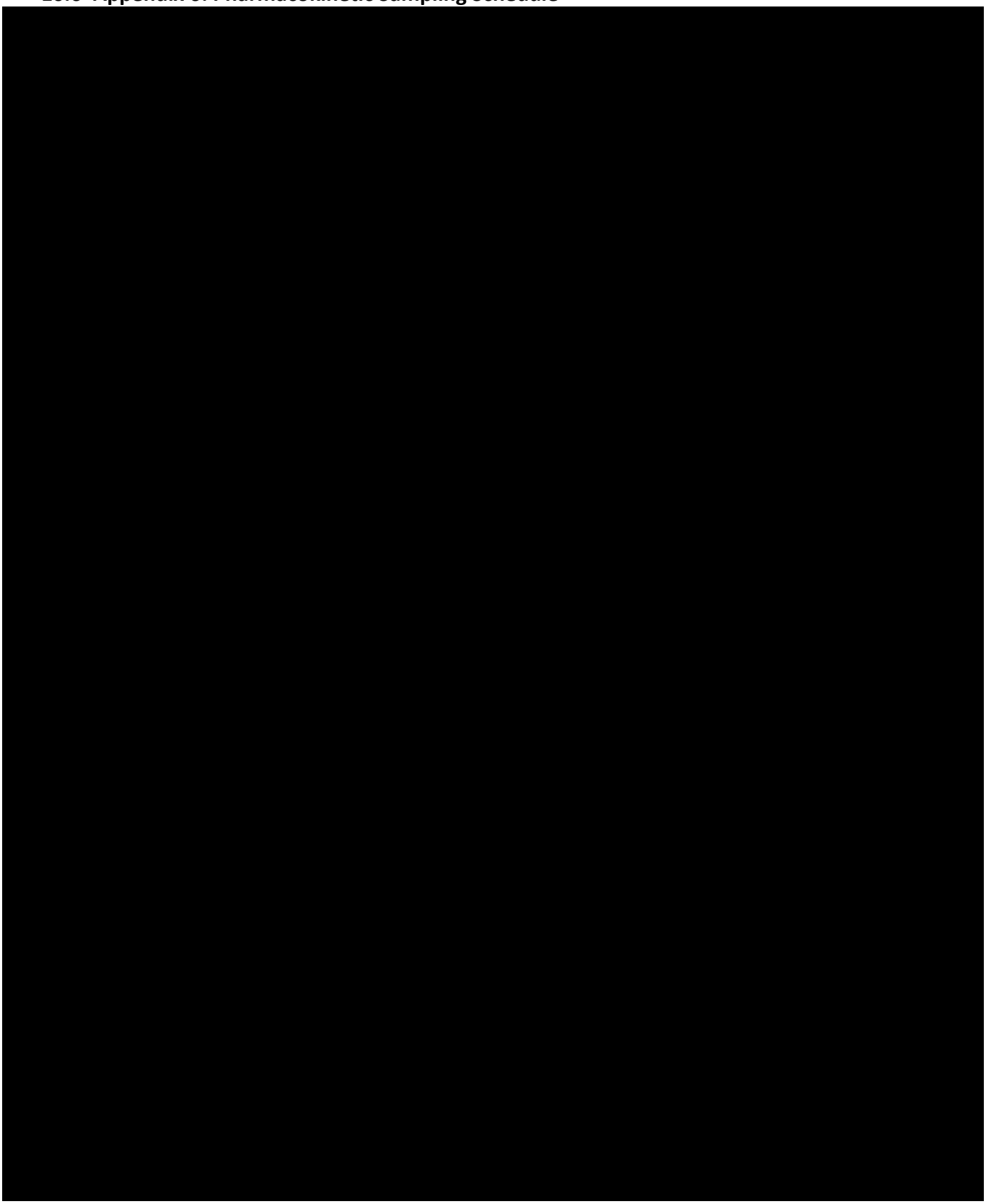
James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-84.

10.5 Appendix 5: Protocol Amendment History

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Indivior. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRB/IEC is notified within 5 days.

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

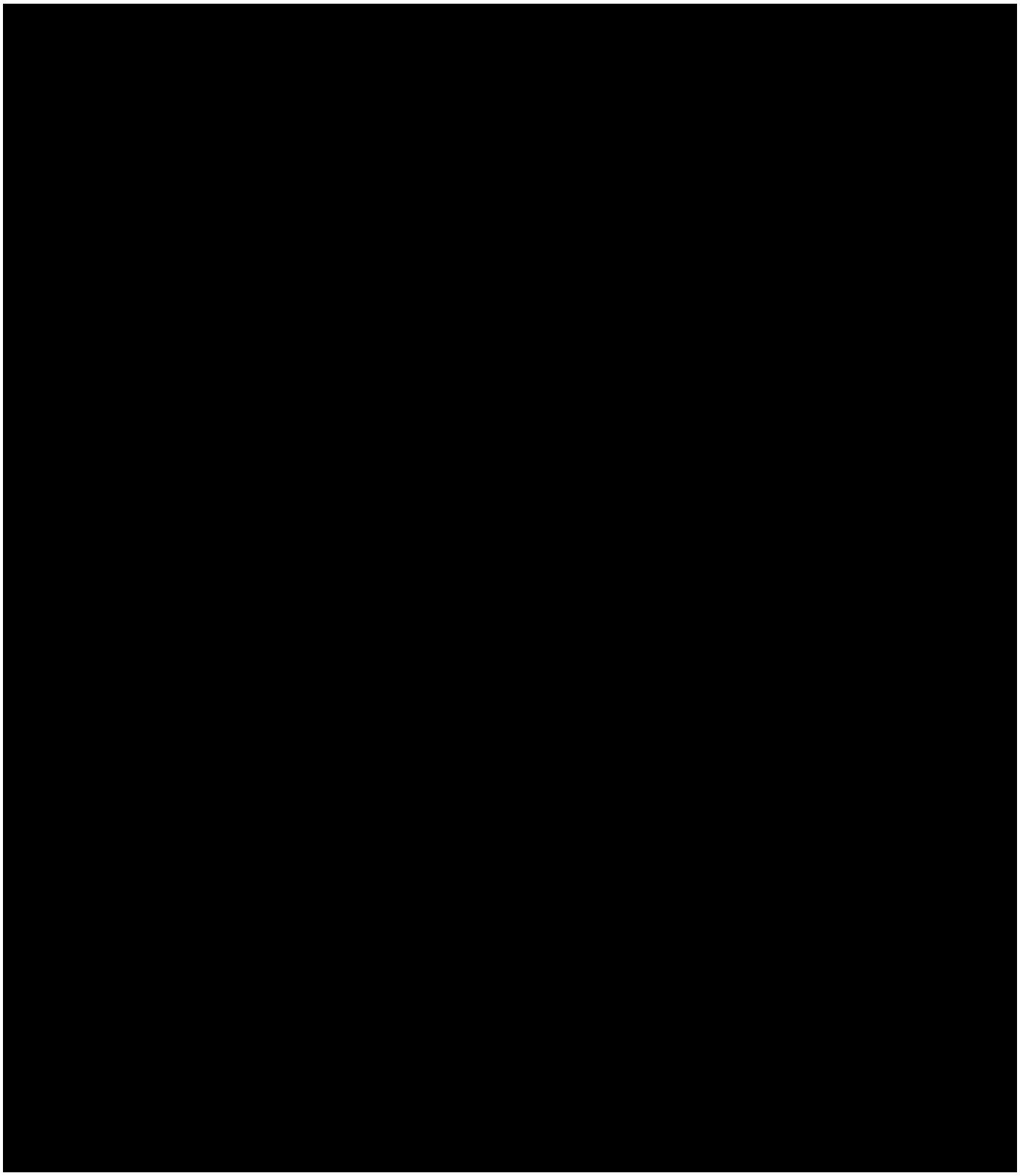
10.6 Appendix 6: Pharmacokinetic Sampling Schedule



[redacted]

Table 7 List of Pharmacokinetic Parameters (non-exhaustive)

[redacted]



10.7 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200 N, Rockville, MD 20852- 1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration Center for Biologics Evaluation and Research
September 2007

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C.262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 CFR Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrolment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (eg, a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (eg, mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorising toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. Background

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterisation of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. Toxicity grading scale tables

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorise adverse events observed during a clinical trial may assist you in monitoring safety and making required reports.

Nonetheless, we believe that categorisation or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added

based on one or more of the following: safety signals observed in preclinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licenced product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non- narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia – beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or <400 gms/24 hours	4 – 5 stools or 400 – 800 gms/ 24 hours	6 or more watery stools or >800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non- narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum[1]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)[2]**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	<125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	>150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	>5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	<3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	<45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine– mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Calcium– hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium– hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	<0.9
Phosphorous– hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	<1.6
CPK– mg/dL	1.25 – 1.5 x ULN[3]	1.6 – 3.0 x ULN	3.1 –10 x ULN	>10 x ULN
Albumin– Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	<2.5	--
Total Protein– Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	<5.0	--
Alkaline phosphate– increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver Function Tests–ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin– when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin– when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes– amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.0 x ULN

[1] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[2] The clinical signs or symptoms associated with laboratory abnormalities might result in characterisation of the laboratory abnormalities as Potentially Life-Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

[3] ULN is the upper limit of the normal range.

Hematology[1]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (Female)- gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< .0
Hemoglobin (Female) change from baseline value- gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> .0
Hemoglobin (Male)- gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC Decrease- cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes Decrease- cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils- cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased- cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN[2]	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	>1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	>1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

[1] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[2] "ULN" is the upper limit of the normal range.

Urine [1]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	>50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

[1] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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